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(21) International Application Number: PCT/US93/04443 (22) International Filing Date: 11 May 1993 (11.05.93) (30) Priority data: 886,049 20 May 1992 (20.05.92) US (60) Parent Application or Grant (63) Related by Continuation US 886,049 (CON) Filed on 20 May 1992 (20.05.92) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : BAKSHI, Raman, K. [IN/US]; 9 Azalea Drive, Edison, NJ 08820 (US). RAS-MUSSON, Gary, H. [US/US]; 155 Park Place, Watchung, NJ 07060 (US). (74) Agent: GRASSLER, Frank, P.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NEW PROCESS FOR PRODUCING 7 β -SUBSTITUTED-4-AZA-5 α -ANDROSTAN-3-ONES (57) Abstract Described is a new process for producing 7 β -substituted-4-aza-5 α -androstan-3-ones and related compounds which are 5 α -reductase inhibitors, consisting of reducing the corresponding androsteneone with lithium and liquid ammonia, contacting the product with an isomerizing agent, oxidizing the product to a seco acid and reacting that seco acid with an amine to cyclize to form 4-aza-5 α -androstan-3-ones.		

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TITLE OF THE INVENTION

NEW PROCESS FOR PRODUCING 7 β -SUBSTITUTED-4-AZA-5 α -
ANDROSTAN-3-ONES

15 BACKGROUND OF THE INVENTION

The present invention is directed to a new process for preparing 7 β -substituted-4-aza-5 α -androstan-3-ones and related compounds and the use of such compounds as 5 α -reductase inhibitors.

20

DESCRIPTION OF THE PRIOR ART

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness
25 and benign prostatic hypertrophy, are the result of hyperandrogenetic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts
30 to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted

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in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been
5 developed, for example, 4'-nitro-3'-trifluoromethyl-isobutyranilide. See Neri, et al., Endo., Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects, are peripherally active, competing
10 with the natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host.

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5 α -dihydrotestosterone, and that it is formed locally
15 in the target organ by the action of testosterone-5 α -reductase. It is also known that inhibitors of testosterone-5 α -reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation.

A number of 4-aza steroid compounds are
20 known in the art as 5 α -reductase inhibitors. For example, see U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson, et al., U.S. Patent 4,845,104 to
25 Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al. which describe 4-aza-17 β -substituted-5 α -androstan-3-ones said to be useful in the treatment of DHT-related hyperandrogenetic conditions.

However, despite the suggestion in the
30 prior art that hyperandrogenetic diseases are the result of a single 5 α -reductase, there are reports

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regarding the presence of other 5 α -reductase isozymes in both rats and humans. For example, in human prostate, Bruchovsky, et al. (See J. Clin. Endocrinol. Metab. 67, 806-816, 1988) and Hudson (see J. Steroid Biochem. 26, p 349-353, 1987) found different
5 5 α -reductase activities in the stromal and epithelial fractions. Additionally, Moore and Wilson described two distinct human reductases with peaks of activities at either pH 5.5 or pH 7-9. (See J. Biol. Chem. 251,
19, p. 5895-5900, 1976.)

10 Recently, Andersson and Russell isolated a cDNA which encodes a rat liver 5 α -reductase (see J. Biol. Chem. 264 pp. 16249-55 (1989). They found a single mRNA which encodes both the liver and prostatic reductases of rats. The sequence of this rat gene was
15 later used to select a human prostatic cDNA encoding a 5 α -reductase termed "5 α -reductase 1". (See Proc. Nat'l. Acad. Sci. 87, p. 3640-3644, 1990.)

20 More recently, a second, more abundant reductase (5 α -reductase 2) has been cloned from human prostate with properties identified with the form found in crude human prostatic extracts. (See Nature, 354, p. 159-161, 1991.)

25 Further, "Syndromes of Androgen Resistance" - The Biology of Reproduction, Vol. 46, p. 168-173 (1992) by Jean O. Wilson indicates that the 5 α -reductase 1 enzyme may be associated with hair follicles.

Thus, the art supports the existence of
at least two genes for 5 α -reductase and two distinct
isozymes of 5 α -reductase in humans. Both forms
30 are present in prostatic tissue in which, 5 α -reductase

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2, is the more abundant, and the other isozyme, 5 α -reductase 1, is believed to be more abundant in scalp tissue.

In the treatment of hyperandrogenetic disease conditions, e.g. benign prostatic hyperplasia (BPH) it would be desirable to have one drug entity which is active against both enzymes 1 and 2 in the prostate to substantially inhibit dihydrotestosterone (DHT) production. Alternatively, it would be desirable to have a drug entity which is highly selective for inhibiting the scalp associated enzyme 5 α -reductase 1, for use in treating diseases of the skin and scalp, e.g. acne and alopecia. This latter drug could also be used in combination with PROSCAR[®] (finasteride) which is highly selective for the prostatic enzyme 5 α -reductase 2 for combination therapy in the treatment of BPH.

New processes are continuously being searched for which are more efficient and environmentally acceptable for producing 7-beta substituted androstane-3-ones, which are active against both alpha reductase enzymes 1 and 2.

SUMMARY OF THE INVENTION

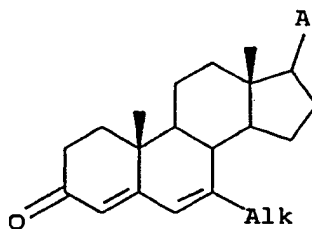
The present invention discloses a novel process for preparing 7 β -substituted-4-aza-5 α -androstan-3-one compounds which are useful for inhibiting the 5 α -reductase isozymes 1 and 2 and are particularly effective in selectively inhibiting the 5 α -reductase-1 associated with the scalp and dually inhibiting both isozymes 1 and 2 in the oral, parenteral or topical treatment of benign prostatic hyperplasia, acne, female

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hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and the prevention and treatment of prostatic carcinoma.

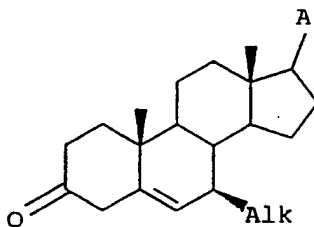
In accordance with the present invention there is provided a process comprising the step of:

a) contacting the compound IV, where Alk is



IV

C₁-C₄ alkyl, allyl, and C₃-C₆ cycloalkyl, and A is a substituent inert under the reaction conditions, with a reducing system comprised of: metallic lithium and liquid ammonia in an inert organic solvent therefor at a temperature in the range of about -45° to -78°C for a sufficient time to stereoselectively produce the 7-beta compound V:

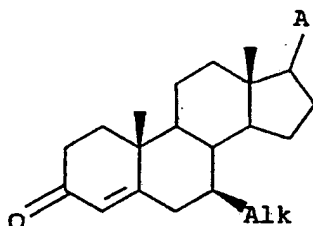


V

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Further provided in the process is the step of:

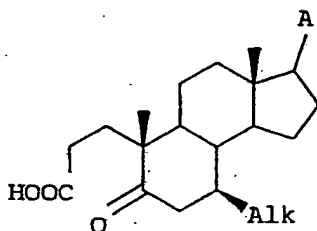
b) contacting compound V with a double bond isomerization agent in an inert organic solvent therefor, at a temperature of 40 to 65°C, under conditions in which the radical A is inert, for a sufficient time to form the isomerized compound VI.



VI.

Also provided in the process is the step of:

(c) contacting compound VI with an oxidizing agent in an inert solvent therefor, at a temperature in the range of 23 to 80°C, under conditions in which radical A is inert, for a sufficient time to form the seco acid VII:

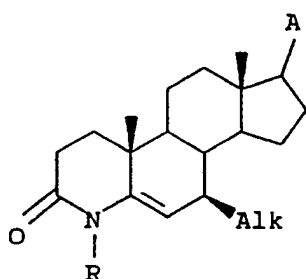


VII.

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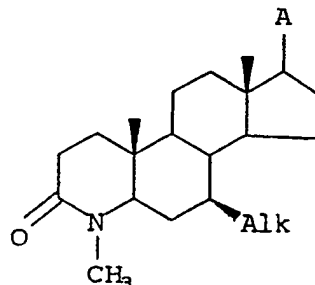
In addition, there is provided the step of:

(d) contacting the seco acid compound VII with an amine of the formula: $R-NH_2$, wherein R is H, C_1-C_4 alkyl, benzyl or allyl, at a temperature of from 100 to 200°C in an inert solvent therefor, under conditions in which A is inert, to form the 4-aza-steroid VIII:

VIII.

Provided also in the process is the step of:

(e) contacting VIII with a platinum catalyst in an inert organic solvent, at room temperature, under conditions where A is inert, for a sufficient time to form the 7-Alk 4-aza steroid VII:

VII.

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Specific embodiments of the process is where Alk is methyl; the reducing system is comprised of metallic lithium and liquid ammonia; the process is carried out in the temperature range which is -78° to -45°C .

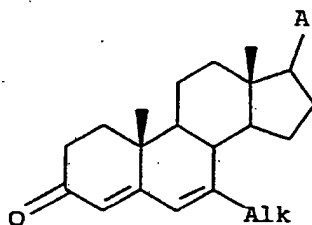
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Also provided is the overall process comprising the steps of:

a) contacting the compound IV, where Alk is

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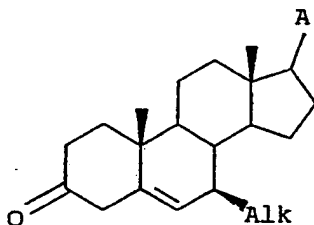
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IV

$\text{C}_1\text{-C}_4$ alkyl, allyl and $\text{C}_3\text{-C}_6$ cycloalkyl, and A is a substituent inert under the reaction conditions, with a reducing system comprised of: metallic lithium and liquid ammonia in an inert organic solvent therefor at a temperature in the range of about -45° to -78°C for a sufficient time to stereoselectively produce the 7-beta compound V:

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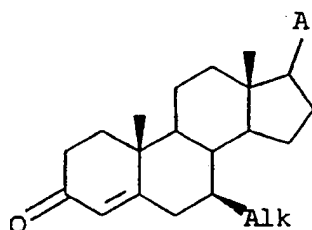
V;

- 9 -

b) contacting compound V with a double bond isomerization agent in an inert organic solvent therefor, at a temperature of 40 to 65°C, under conditions in which the radical A is inert, for a sufficient time to form the isomerized compound VI.

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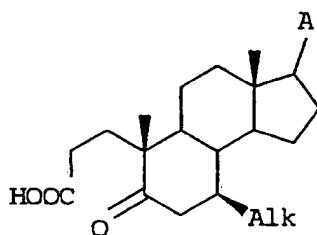
VI;

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(c) contacting compound VI with an oxidizing agent in an inert solvent therefor, at a temperature in the range of 23 to 80°C, under conditions in which radical A is inert, for a sufficient time to form the seco acid VII:

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VII;

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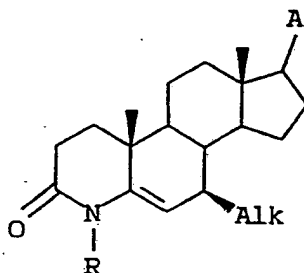
(d) contacting the seco acid compound VII with an amine of the formula: $R-NH_2$, wherein R is H,

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C₁-C₄ alkyl, benzyl or allyl, at a temperature of from 100 to 200°C in an inert solvent therefor, under conditions in which A is inert, to form the 4-aza-steroid VIII:

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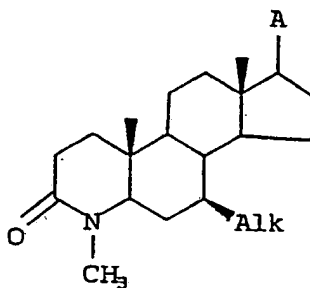
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VIII;

(e) contacting VIII with a platinum catalyst in an inert organic solvent, at room temperature, under conditions where A is inert, for a sufficient time to form the 7-Alk 4-aza steroid VII:

20

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VII.

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DETAILED DESCRIPTION OF THE
INVENTION AND PREFERRED EMBODIMENTS

By the term "C₁-C₄ alkyl" as used herein,
is meant to include: e.g. methyl, ethyl, propyl,
5 isopropyl, n-butyl, sec-butyl, isobutyl and t-butyl.

By the term "C₃-C₆ cycloalkyl" as used
herein is meant to include cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl.

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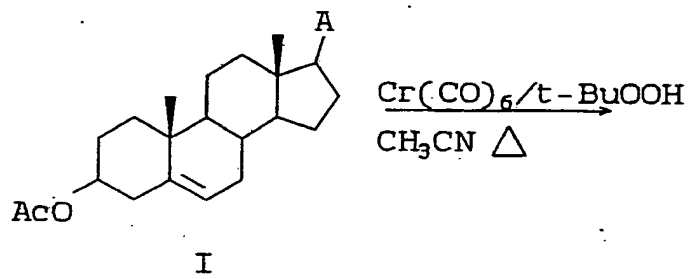
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The process of this invention is illustrated
in the following Flowsheets:

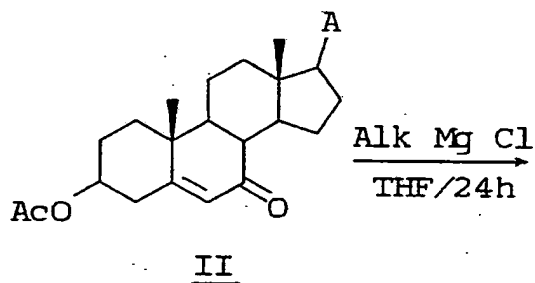
GENERAL FLOWSHEET

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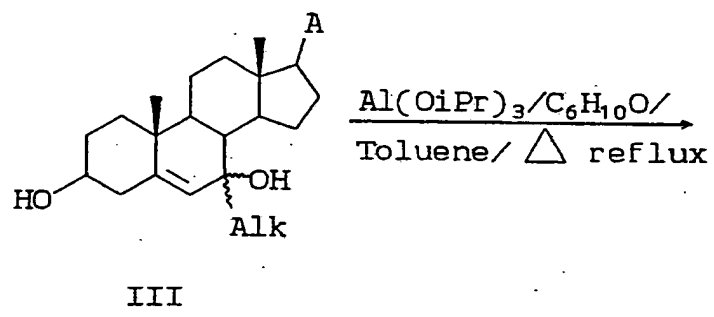


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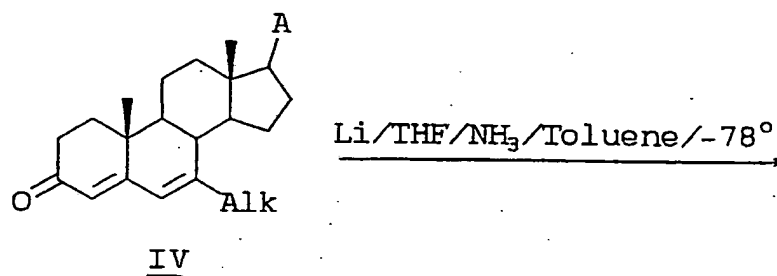


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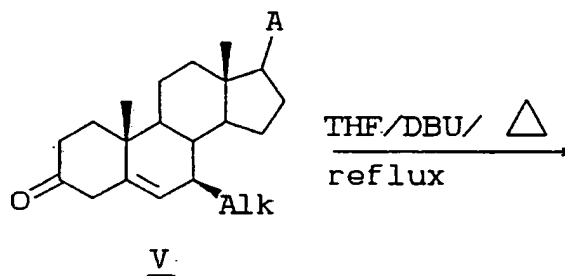
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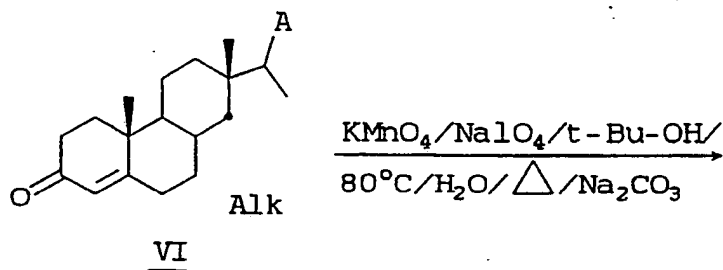
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GENERAL FLOWSHEET (Cont'd.)

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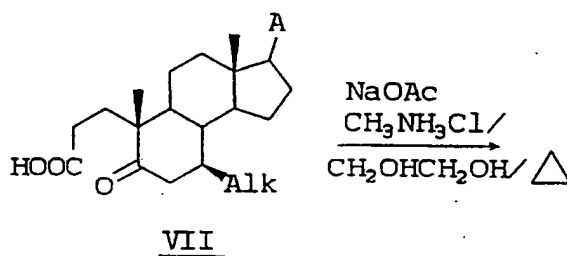


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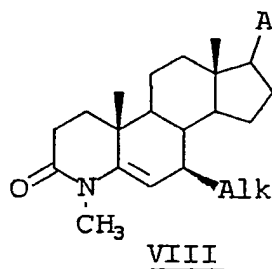
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7-Beta Alkyl-17-A Series

The compounds produced by the instant invention also include a 7 β alkyl group, e.g. methyl, ethyl, isopropyl, t-butyl, allyl, where A is defined below, can be prepared by the procedure outlined in The General Flowsheet.

The term "Alk" as used herein being the 7-beta substituent in the formula signifies C₁-C₄ linear or branched alkyl, e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, and cycloalkyl.

The "Alk" substituent can be introduced onto the B ring of the 4-aza steroid generally by the application of an organometallic carbonyl addition reaction, e.g. the Grignard reaction in which the 7-carbonyl group can be reacted with the Grignard reagent containing "Alk" as the R radical in RMgX. Also applicable in the process are carbonyl addition reactions utilizing lithium and zinc organometallic reagents which are known in the art.

The term "A" is the 17-substituent which can be any substituent preferably inert and non-interfering under the particular reaction conditions of each step outlined in the following General Flowsheet.

The A group can also be a protected hydroxy or protected amino group which undergoes the indicated reaction sequence and then is subsequently removed, or it can also be removed during a particular step providing it does not interfere with the indicated reaction. For example, where A is 17-O-TBDMS, i.e., t-butyl-dimethylsilyloxy, the silyl protecting group can be removed during e.g., the ring closure step of the

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seco acid VII to the 4-aza steroid VIII, such that the subsequent steps are performed on the 17-OH compound. Also, the starting A group can be a precursor to the finally desired A group and be converting thereto concurrently in one of the steps. For example, where A
5 contains a double bond, e.g., a stigmasterol analog, the double bond in the 17-side chain may also be oxidized during the seco acid formation in going from VI to VII.

Representative examples of the 17-A group
10 include H, protected hydroxy, e.g. dimethyl-t-butyl silyloxy, hydroxy, protected amino, e.g. acetylamino, amino, C₁-C₁₀ alkyl, e.g. methyl, ethyl, 6-methyl-hept-2-yl (cholestanyl 17-side chain), stigmasterol side chain, aryl substituted C₁-C₁₀ alkyl, e.g.
15 omega-phenylpropyl, heteroaryl substituted C₁-C₁₀ alkyl, e.g. omega-(4-pyridyl)-butyl, carboxylic ester, e.g. carbomethoxy, carboxamide, e.g. N,N-diisopropyl carboxamide, carboxylic acid, carbamates, e.g. t-butylcarbonylamino ureas, e.g. n-t-butylcarbonyl-
20 amino, ethers, e.g. n-butyloxy- and the like.

The starting materials for the process generally are the 3-acetoxy-androst-5-enes which are known and available in the art.

As seen in the Flowsheet, using general
25 formulas, where A is described above, the starting 3-acetoxy-androst-5-en-17-A I is oxidized to the corresponding 5-en-7-one II by treatment with e.g. hydrogen t-butyl peroxide and chromium hexacarbonyl in e.g. acetonitrile, at reflux. Other solvents which
30 can be used include propionitrile, butyronitrile. The temperature for the reaction is generally carried out

- 17 -

with range of 40 to 85°C and the reaction is carried out under dry conditions and generally requires about 24 hours for completion.

5 The Alk group, e.g. methyl, ethyl, allyl, phenyl, can be introduced at this point by an organo-metallic carbonyl addition reaction, e.g. Grignard reaction using e.g., methyl, allyl or cycloalkyl magnesium chloride in e.g., anhydrous THF at 0-23°C to produce the 7-Alk-7-hydroxy adduct III. The Grignard reaction conditions are conventional and include the use of methyl magnesium chloride, ethyl magnesium bromide, allyl magnesium chloride, cyclopropyl magnesium bromide, and the like. Other usable dry solvents include diethyl ether, dimethoxyethane, di-n-butyl ether. The reaction is conducted under dry conditions generally in the temperature range of 0 to 40°C. Generally, the reaction requires about 6 to 24 hours for completion. Other organometallic carbonyl addition reactions can be used.

20 The adduct III is then oxidized with e.g. aluminum isopropoxide and cyclohexanone (Oppenauer oxidation conditions) in e.g. refluxing toluene solvent to produce the 7-alkyl-4,6-dien-3-one IV. Other reagents which can be used are aluminum ethoxide or aluminum t-butoxide. Other solvents which can be used are methylethylketone and xylene. The temperature range is generally in the range of 60 to 120°C, the reaction carried out under anhydrous conditions and generally requires about 2 to 24 hours for completion.

30 The next step is a key step in which the Grignard adduct IV is reduced with metallic lithium, liquid ammonia, THF and toluene at -78°C

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to stereoselectively yield the 7-beta-alkyl-5-en-3-one V. Other metals which can be used in this reduction are: sodium, potassium, and calcium. Other amines which can be used are methylamine and ethylamine. Other solvents which can be used are: n-butylether, and dimethoxyethane. The reaction is generally carried out under anhydrous conditions in the temperature range of 23°C to -78°C and requires about 2-10 hours to go to completion.

In the next step the delta-5 double bond is isomerized to the 4-ene VI by the use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in, e.g. refluxing tetrahydrofuran (THF) to produce 7-alkyl 4-en-3-one. Other isomerization reagents which can be used include: diisopropylethylamine and DBN (Aldrich), being 1,5-diazabicyclo[4.3.0]non-5-ene. Other solvents which can be used include: toluene, dimethylether. The reaction is generally carried out under dry conditions at a temperature range of 40 to 65°C and generally requires 1-2 hours for completion.

The A Ring is next cleaved by treatment with e.g. potassium permanganate, sodium periodate in e.g., t-butylalcohol at 80°C to produce the corresponding seco-acid VII. Other oxidation reagents which can be used include ruthenium tetroxide and ozone. Other solvents which can be used are: CH₃CN, CCl₄, MeOH and CH₂Cl₂. The reaction generally requires about 2 to 4 hours to proceed to completion.

Treatment of the seco-acid with an appropriate amine e.g., methylamine hydrochloride and sodium acetate in ethylene glycol at 180°C, yields e.g., the 4-methyl-4-aza-androst-5-en-3-one VIII.

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Other amines which can be used are ethylamine, ammonium acetate, substituted benzylamines, e.g. 4-methoxybenzylamine, and the like. Other solvents applicable in the reaction include: acetic acid, xylene. The reaction is generally carried out at a temperature in the range of 100 to 200°C and generally requires about 2-8 hours to proceed to completion.

Structure VIII in turn is catalytically hydrogenated with e.g., Pt, to reduce the 5-delta double bond to produce the 5 α -hydrogen compound IX. The solvent for the reduction is usually acetic acid but also useful is EtOH. The catalysts for this hydrogenation also include Pd/C and noble metals e.g. nickel. The hydrogenation is usually carried out in a shaker hydrogenation apparatus at room temperature under a H₂ pressure of 40 to 2000 psig. and generally requires about 1-24 hours to proceed to completion.

The seco-acid VII can be similarly treated with ammonia generated from ammonium acetate to produce the corresponding N-H compound, X, which can then be analogously treated as above with catalytic Pt in a hydrogen atmosphere to produce the corresponding 5 α -4N-H compound XI.

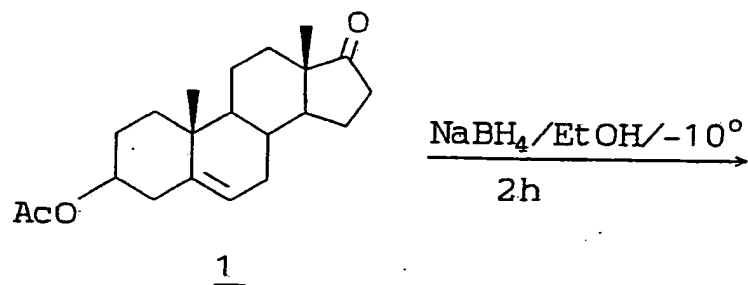
Throughout this series of reactions, the 17-A group should be inert or non-interfering to the individual reaction conditions for placing the 7-substituent onto the steroid B ring.

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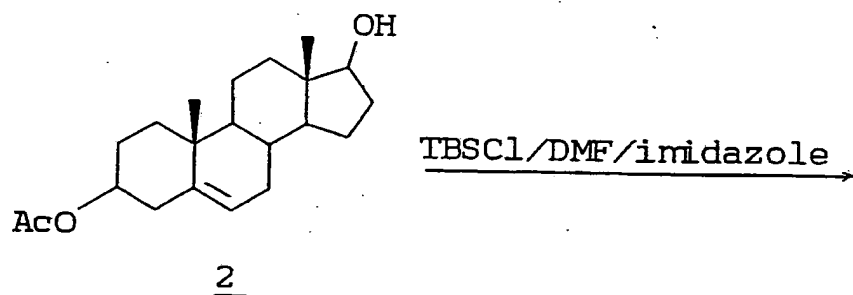
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FLWSHEET A

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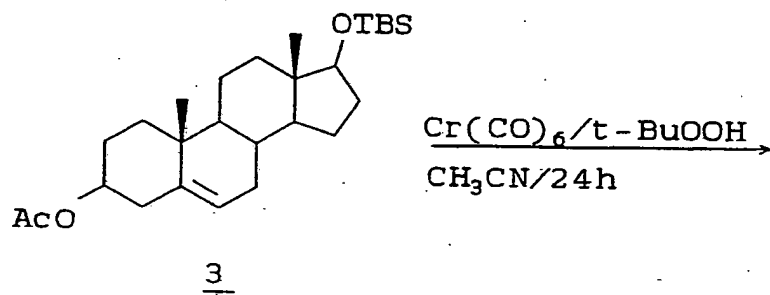


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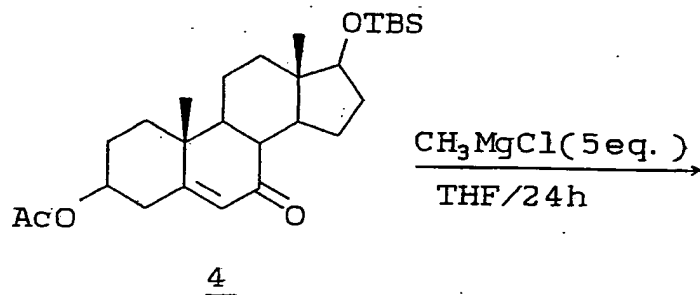
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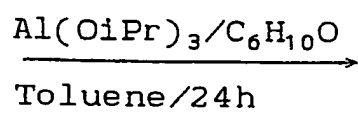
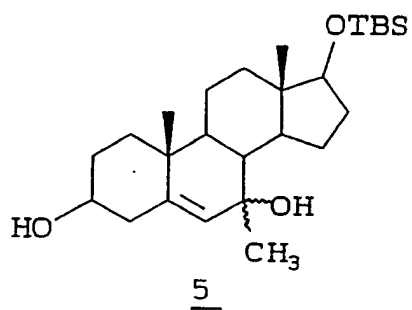
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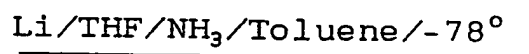
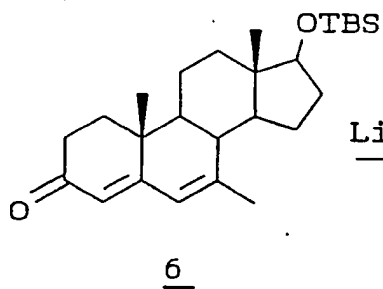
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FLOWSHEET A (Cont'd.)

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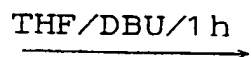
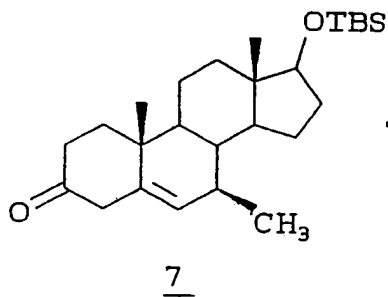


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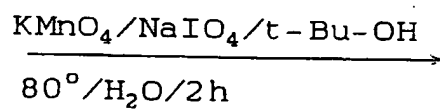
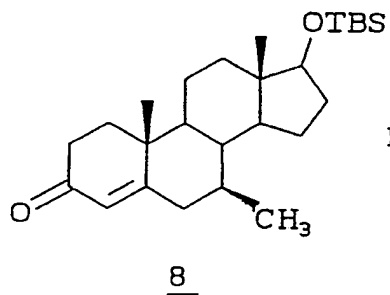
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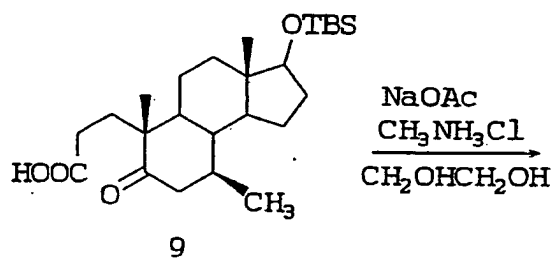
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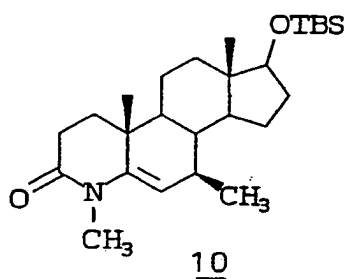
- 22 -

FLWSHEET A (Cont'd.)

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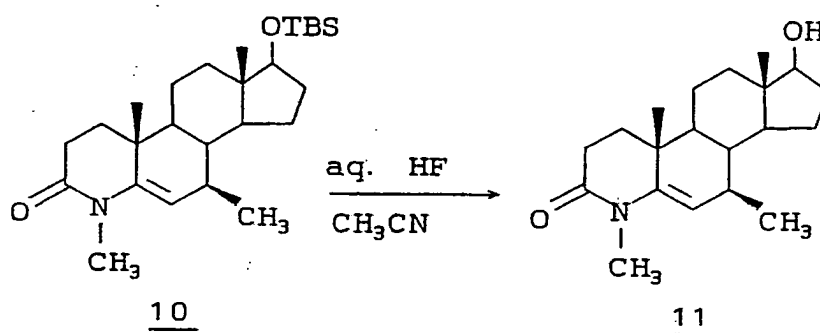
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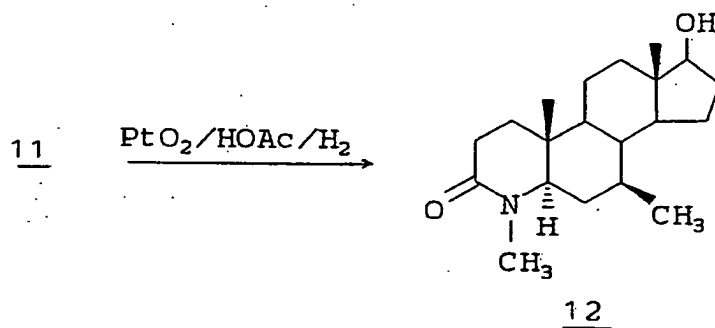
FLWSHEET B

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7-Beta Alkyl-17-Oxy-Androstanes

The process of the instant invention is also applicable, e.g. where 17-A is hydroxy or protected hydroxy. The appropriate 7 β alkyl group, e.g. methyl, ethyl, isopropyl, can be introduced by the procedure outlined in Flowsheets A and B.

As seen in Flowsheet A, the 3-acetoxy-androst-5-en-17-one 1 is reacted with sodium borohydride in a suitable solvent, e.g. ethanol, at -10°C to stereospecifically reduce the 17-ketone to the 17 β -ol 2. The 17-hydroxy group is protected with the TBS group (t-butyldimethylsilyl) by reacting TBS chloride with 2 in a suitable solvent, e.g. DMF in the presence of the proton acceptor, e.g. imidazole, at room temperature, to form 3.

Following the hydroxy protection, this compound is oxidized in the seven position to the corresponding 5-en-7-one 4 by treatment of 3 with hydrogen t-butyl peroxide and chromium hexacarbonyl in e.g. acetonitrile, at reflux. The alkyl group, e.g. methyl, can be introduced at this point by a Grignard reaction using e.g., methyl magnesium chloride in anhydrous THF at 0-10°C to produce the 7-methyl-7-hydroxy adduct 5. This Grignard product is then oxidized with aluminum isopropoxide and cyclohexanone (Oppenauer oxidation conditions) in refluxing toluene solvent to produce the 7-methyl-4,6-dien-3-one 6. This in turn is reduced using metallic lithium, in liquid ammonia, THF and toluene at -78°C to selectively yield the 7-beta-methyl-5-en-3-one 7. In the next step the delta-5 double bond is isomerized to the 4-ene by use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in refluxing tetrahydrofuran (THF) to produce the 4-en-3-one,

- 24 -

8. The A Ring is next cleaved by treatment with potassium permanganate, sodium periodate in t-butyl alcohol at 80°C to produce the corresponding seco-acid

9. Treatment of the secoacid 9 with an appropriate amine e.g., methylamine hydrochloride and sodium acetate in ethylene glycol at 180°C, yields the 4-aza-androst-5-en-3-one 10. The TBS protecting group is then removed e.g., by aqueous HF in acetonitrile at 0°C, to yield the 17-B alcohol 11. This in turn is selectively reduced to remove the 5-delta double bond to produce the 5 α -hydrogen compound 12.

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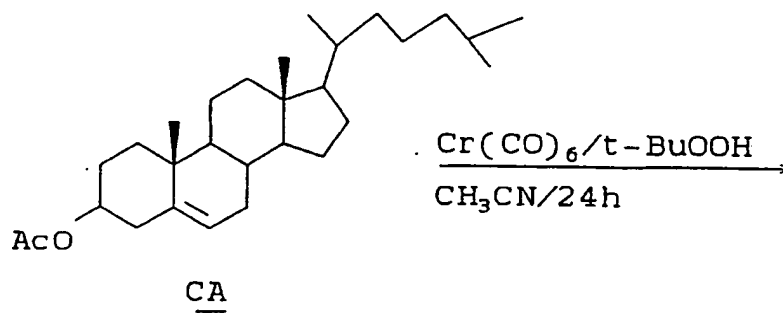
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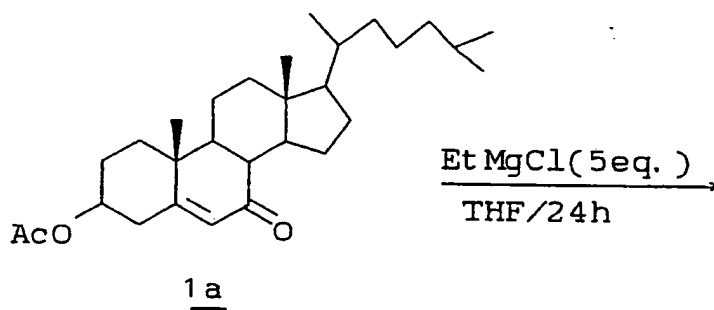
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FLOWSHEET C

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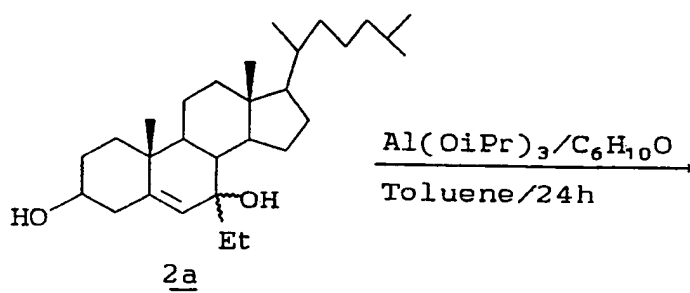


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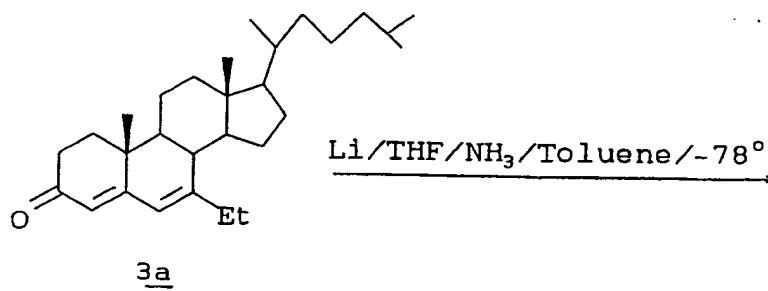
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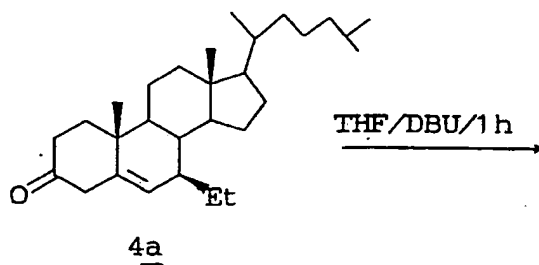
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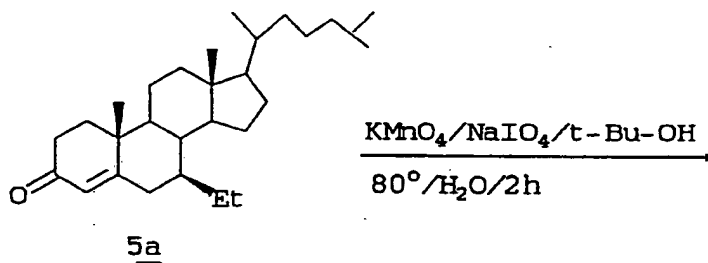
- 26 -

FLOWSHEET C (Cont'd.)

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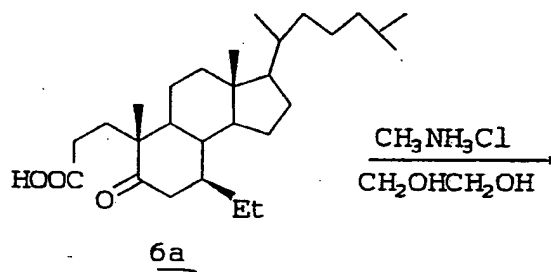


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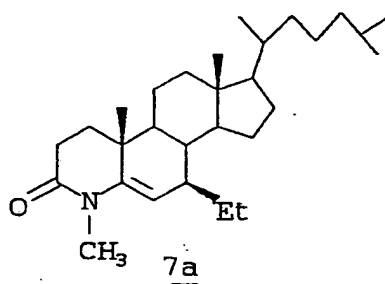
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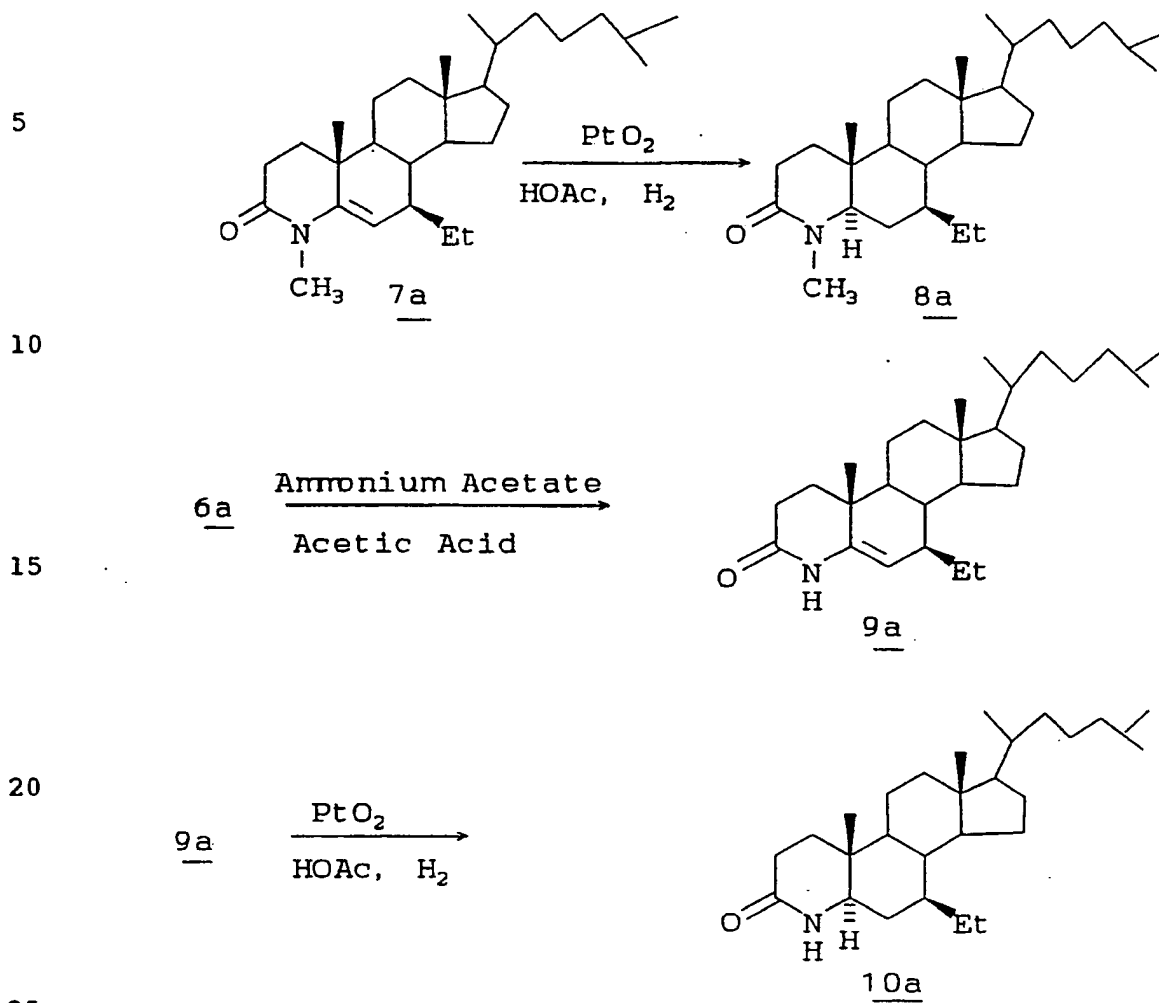


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FLWSHEET D7-Beta-Ethyl-Cholestane Analogues

The 7-ethyl substituent is introduced into the cholestane series as illustrated in Flowsheets C and D by the same analogous procedure as described in the General Flowsheets and A and B.

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The starting cholesteryl acetate CA is available commercially (Aldrich). This is treated using the analogous chromium hexacarbonyl/hydrogen t-butylperoxide/acetonitrile oxidation procedure (described in JCS Perkin Trans. 1985, p. 267 by A. J. Pearson) to yield the 3-acetoxy-cholest-5-en-7-one 1a. This can be reacted with an alkyl Grignard reagent, e.g. ethyl magnesium chloride to form the adduct 2a. This is oxidized under Oppenauer conditions to yield the dienone 3a, which then can undergo metal-ammonia reduction to yield the 7 β -ethyl-5-en-3-one, 4a. This is isomerized using DBU to the 4-en-3-one, 5a, which is oxidized to open Ring A to yield the seco-acid 6a. This can be treated with amines, e.g. methylamine, to yield the A-ring closed 4-methyl-4-aza compound 7a. This in turn can be catalytically hydrogenated to yield the 7-ethyl-5-alpha-4-methyl-4-aza-cholestan-3-one, 8a.

Similarly, by treatment of the seco-acid 6a with ammonium acetate/acetic acid, the corresponding 4-NH analog 9a, is produced which can be catalytically hydrogenated to yield the 7-beta-ethyl-5 α -4-aza-cholestan-3-one, 10a.

The above defined 7-substituents can be introduced into all of the compounds defined for the 17-A group herein by appropriate analogous procedures.

The following examples are illustrative of representative embodiments of this invention and should not be construed to be limits on the scope or spirit of the instant invention.

The R_f values cited were carried out on standard thin layer chromatographic Si gel plates. The elution solvent system used is given in the parentheses following the R_f value.

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The mass spectral values are given either as FAB, i.e., fast atom bombardment, and are reported as (M+1) molecular ion peaks, being the molecular weight plus one atomic mass unit. The electron impact (EI) mass spectrum values are reported as molecular ion peaks and are indicated in parentheses, either being (M) or (M+2), the molecular weight, MW, or the MW plus two atomic units.

The nuclear magnetic resonance data was taken at 400 MHz in CDCl₃ and is tabulated for unique proton values of each compound at the end of the Examples. The coupling constant J is given in Hertz (Hz) units.

EXAMPLE 1

Synthesis of 3-Acetoxy-Androst-5-en-17-ol (2)

To a solution of 100 mg. (0.303 mmol) of 3-acetoxy-androst-5-en-17-one, 1, in 3 ml EtOH at -10°C, was added 22.9 mg (0.606 mmol) of sodium borohydride with stirring. After the reaction mixture was stirred for one and ½ hours, the mixture was diluted with 10 ml water, the ethanol solvent removed under vacuum, and the residue extracted with ethyl acetate. The organic layer was washed with aqueous Na₂CO₃, brine, dried over sodium sulfate and concentrated to leave a residue of crude title compound 2. Proton NMR confirmed the assigned structure.

- 30 -

EXAMPLE 2Synthesis of 3-Acetoxy-Androst-5-en-17-ol, 17-t-butyl-dimethylsilyl ether (3)

5 To a solution of the androstan-17-ol, 2,
from Example 1, being 4.5 g (13.55 mmol) in 50 ml.
dimethylformamide at 23°C was added 2.76 g (40.65
mmol) imidazole followed by 3.063 g (20.32 mmol) of
t-butyldimethylsilyl chloride. The reaction mixture
10 was stirred and a solid began to precipitate. Twenty
additional ml of DMF were added and the mixture
further stirred overnight. The mixture was poured
into 1 liter water, the solid filtered and washed with
water. The solid was dissolved in ethylacetate, the
15 organic layer washed with brine and dried over sodium
sulfate, concentrated to yield the silyl protected 7-ol
title compound 3. The proton NMR confirmed the
assigned structure.

EXAMPLE 3

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Synthesis of 3-Acetoxy-Androst-5-ene-7-one-17 β -ol,
17-t-butyldimethylsilyl ether (4)

To a solution of the TBMS protected 17-ol
3 from Example 2, being 5.6 g (12.55 mmol) in 100 ml
25 acetonitrile at 23°C was added 90% t-butyl hydrogen
peroxide, 3.958g (43.92 mol), and 138 mg chromium
hexacarbonyl. After refluxing the mixture under nitro-
gen for 24 hours, the reaction mixture was poured into
one liter water, solid was filtered, the residue washed
30 with 500 ml water and the residue dissolved in 350 ml
methylene chloride. The organic layer was washed with

- 31 -

brine, dried over sodium sulfate and concentrated to yield crude material. Thin layer chromatography (3:1 hexane/ethyl acetate on silica gel) showed the presence of starting material. The solid was purified by column chromatography over silica gel by elution with 7% ethyl acetate/hexane to yield the title compound 4. Proton NMR confirmed the assigned structure.

EXAMPLE 4

10 Synthesis of 3,7-Dihydroxy-7-methyl-Androst-5-en-17B-ol, 17-TBMS ether (5)

 To a solution of the product 4 from Example 3, being 440 mg. (0.956 mmol) in dry tetrahydrofuran at 0°C was added dropwise methyl magnesium chloride over 5-10 minutes. The reaction mixture was then allowed to stir at room temperature for 24 hours, then poured into saturated aqueous ammonium chloride. The THF solvent was removed under vacuum and the aqueous phase extracted with ethyl acetate. The organic layer was washed with brine, dried, concentrated to yield crude product. Proton NMR confirmed the assigned structure of the title compound 5 which was used in the next step without further purification.

25

EXAMPLE 5

Synthesis of 7-methyl-Androst-4,6-dien-3-one-17-ol, 17-t-butyldimethylsilyl ether (6)

 The above Grignard product 5, 3.5g. (7.142 mmol) was dissolved in 50 ml toluene/50 ml. cyclohexanone and 20 ml of solvent distilled off under

- 32 -

vacuum. To this was added 4.54 g. aluminum isopropoxide and the reaction mixture refluxed overnight for 15 hours. The mixture was cooled, diluted with ethyl acetate, washed with sodium potassium tartarate, brine, and the organic layer was concentrated under vacuum and the residue steam distilled. The residue was extracted with ethyl acetate, washed with brine, dried and purified by column chromatography on silica gel, eluting with 5% EtOAc/hexane to yield the title compound 6.

EXAMPLE 6

Synthesis of 7 β -Methyl-Androst-5-en-3-one-17-ol, t-Butyldimethylsilyl ether. (7)

To a solution of 370 mg of 6, from Example 5, in 5.5 ml ammonia, 1 ml THF, 1 ml. toluene, was added 50 mg. of metallic lithium in small pieces. After stirring the blue solution for 2 hours, a solution of 1,2-dibromethane in 2 ml THF was added. After stirring the solution at -78°C for 10 minutes, 250 mg of ammonium chloride was added and the mixture stirred for 10 minutes. The excess ammonia was removed by evaporation under a nitrogen steam. The reaction mixture was diluted with brine, extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to yield crude material 7 which was used as such in Example 7.

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EXAMPLE 7

Synthesis of 7 β -Methyl-Androst-4-en-3-on-17-ol,
t-Butyldimethylsilyl ether, (8)

5 To a solution of 7, from Example 6, being
432 mg in 4 ml THF was added 150 microliters DBU
(1,8-diazabicyclo[5.4.0] undec-7-ene under nitrogen
with stirring. The mixture was refluxed for 1.5 hours,
then cooled, diluted with NH₄Cl solution. The solvent
THF was removed under vacuum and the residue extracted
10 with ethyl acetate. The organic layer was washed with
brine, dried and concentrated under reduced pressure to
yield crude material. The titled product 8 was puri-
fied by chromatography on silica gel using 10% EtOAc/
hexane as eluant.

15

EXAMPLE 8

Synthesis of 17 β -(t-butyldimethylsilyloxy)-7 β -methyl-
5-oxo-A-nor-3,5-secoandrostan-3-oic acid, (9)

20 To a solution of 884 mg of 8 in 15 ml.
t-butyl alcohol at 80°C was added 248 mg sodium
carbonate in 1.5 ml water followed by a dropwise
addition over 15-20 minutes of a mixture of 2.273 g
sodium periodate with 16.8 mg potassium permanganate in
25 8 ml. water. The reaction mixture was heated at 80°C
for 2 hours, cooled, filtered, the residue washed with
water, and then the extract concentrated under vaccum.
The extract was acidified with aqueous HCl, extracted
with ethyl acetate and the organic layer washed with
30 aqueous NaHSO₃, brine, dried and concentrated to yield
crude 9. The proton NMR confirmed the assigned
structure.

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EXAMPLE 9

Synthesis of 4,7-Dimethyl-4-aza-Androst-5-en-3-one-17-ol, t-butyldimethylsilyl ether. (10)

5 To a solution of 9, 840 mg in 5 ml
ethylene glycol was added 1.5 g sodium acetate and
737 mg. methylamine hydrochloride. After stirring
the reaction mixture 4 hours at 180°C, the mixture
was cooled, diluted with water, extracted with ethyl
10 acetate, dried and concentrated to afford crude title
compound 10. Proton NMR confirmed the assigned
structure.

EXAMPLE 10

15

Synthesis of 4,7-Dimethyl-4-aza-Androst-5-en-3-one-
17-ol. (11)

To a solution of 700 mg of 10 from Example
9, in 20 ml of acetonitrile at 0°C was added 500 micro-
20 liters aqueous HF. After stirring the reaction mixture
for one hour, the HF was neutralized with aqueous
sodium carbonate, diluted with water, acetonitrile
removed under vacuum, and the residue extracted with
ethyl acetate. The organic layer was dried, concen-
25 trated to give crude title compound 11 which was
further purified by preparative chromatography on
silica gel using 3:1 chloroform/acetone.

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EXAMPLE 11Synthesis of 4,7-dimethyl-4-aza-androstan-3-one-17-ol. (12)

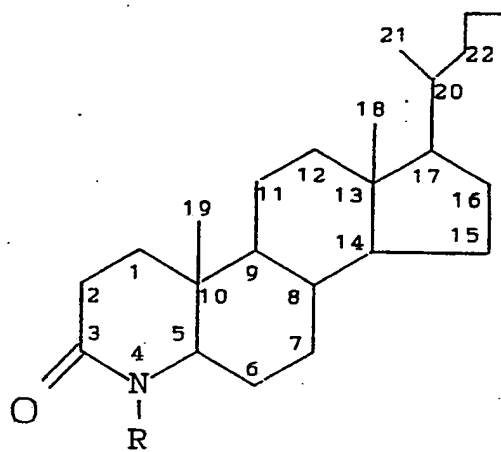
5 To a solution of 11 from Example 10, being
350 mg in 10ml acetic acid was added 100 mg catalytic
platinum dioxide and the resulting mixture was evacu-
ated and flushed with hydrogen. The reaction was
shaken overnight at room temperature under 40 Psig
hydrogen pressure. The solution was filtered and
10 concentrated to a residue. The residue was worked
up with ethyl acetate, the organic layer was then
concentrated under vacuum, diluted with ethyl acetate,
washed with aqueous NaHCO₃, brine, dried, concentrated
to yield the title compound 12.
15 Mass Spec: 320,(M+1).

The following Table lists the unique proton
NMR values (400 MHz in CDCl₃) for each compound. The
data are reported as: s = singlet, d = doublet, m =
multiplet, J = coupling constant. The absorption
20 values are given del (δ) units and are illustrated for
the C-18, C-19 and C-21 angular ring methyl protons and
protons associated with unique portions of the molecule.

The numbering of the steroid is given by the
following structure:
25

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NMR DATA

	Compound <u>No.</u>	<u>C-18 CH₃</u>	<u>C-19 CH₃</u>	<u>Others</u>
5	2	0.72	1.02	3 OAc, 3H, s, 2.02 17H, 1H, t, 3.65, J=8.5
10	3	0.70	1.02	3 OAc, 3H, s, 2.02 17H, 1H, t, 3.55, J=8.5
15	4	0.72	1.21	3 OAc, 3H, s, 2.04 17H, 1H, t, 3.55 J=8.5
20	5	0.72	0.95 1.20	7 Me, 3H, s, 1.12 1.21 17H, 1H, m, 3.55
	6	0.80	1.08	7 Me, 3H, s, 1.9 6H, 1H, s, 5.68 4H, 1H, s, 5.92
25	7	0.72	1.12	7 Me, 3H, d, 0.96 J=6.6 6H, 1H, m, 5.08
30	8	0.72	1.17	7 Me, 3H, d, 1.03 J=6.5 4H, 1H, s, 5.68

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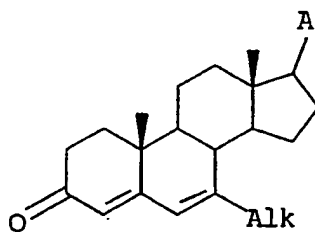
Compound		<u>C-18 CH₃</u>	<u>C-19 CH₃</u>	<u>Others</u>
	<u>No.</u>			
5	9	0.72	1.04	7 Me, 3H, d, 0.95 J=6.5
	10	0.72	1.02	7 Me, 3H, d, 1.04 J=6.5 6H, 1H, d, 4.78 J=3
10	11	0.78	1.02	7 Me, 3H, d, 1.06, J=6.5 6H, 1H, d, 4.79, J=3
15	12	0.74	0.86	7 Me, 3H, d, 1.02, J=6.5 5H, 1H, dd, 3.10 J=4.5 J=13.5
20				
25	8a	0.690	0.830	21-CH ₃ , d, 0.900 J=7 N-CH ₃ , s, 2.93
	10a	0.675	0.808	21-CH ₃ , d, 0.893 J=7 5H, m, 2.97-3.13
30				

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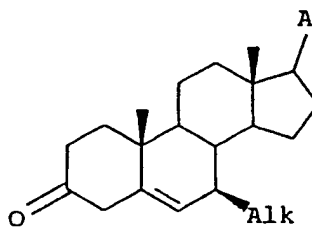
WHAT IS CLAIMED IS:

1. A process comprising the step of:

a) contacting the compound IV, where Alk is

IV

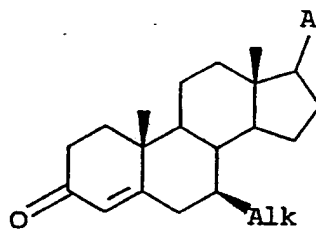
C₁-C₄ alkyl, allyl, and C₃-C₆ cycloalkyl, and A is a substituent inert under the reaction conditions, with a reducing system comprised of: metallic lithium and liquid ammonia in an inert organic solvent therefor at a temperature in the range of about -45° to -78°C for a sufficient time to stereoselectively produce the 7-beta compound V:

V.

- 40 -

2. The process of Claim 1 further comprising the step of

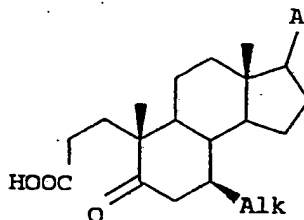
b) contacting compound V with a double bond isomerization agent in an inert organic solvent therefor, at a temperature of 40 to 65°C, under conditions in which the radical A is inert, for a sufficient time to form the isomerized compound VI.



VI.

3. The process of Claim 1 further comprising the step of:

(c) contacting compound VI with an oxidizing agent in an inert solvent therefor, at a temperature in the range of 23 to 80°C, under conditions in which radical A is inert, for a sufficient time to form the seco acid VII:

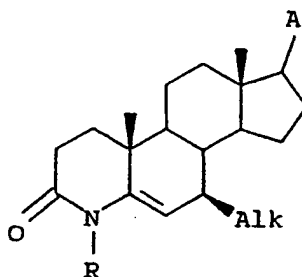


VII.

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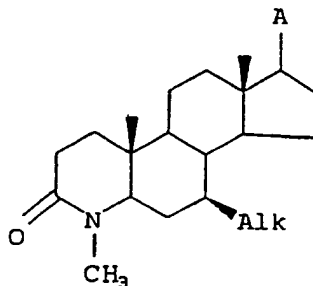
4. The process of Claim 3 further comprising the step of:

(d) contacting the seco acid compound VII with an amine of the formula: $R-NH_2$, wherein R is H, C_1-C_4 alkyl, benzyl or allyl, at a temperature of from 100 to 200°C in an inert solvent therefor; under conditions in which A is inert, to form the 4-aza-steroid VIII:

VIII.

5. The process of Claim 4 further comprising the step of:

(e) contacting VIII with a platinum catalyst in an inert organic solvent, at room temperature, under conditions where A is inert, for a sufficient time to form the 7-Alk 4-aza steroid VII:

VII.

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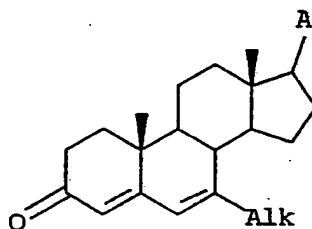
6. The process of Claim 1 in which Alk is methyl.

7. The process of Claim 1 in which the reducing system is comprised of metallic lithium and liquid ammonia.

8. The process of Claim 1 in which the temperature range is -78° to -45°C .

9. The process of Claim 1 comprising the steps of:

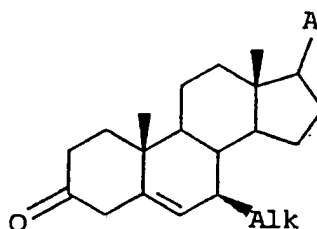
a) contacting the compound IV, where Alk is



IV

$\text{C}_1\text{-C}_4$ alkyl, allyl, and $\text{C}_3\text{-C}_6$ cycloalkyl, and A is a substituent inert under the reaction conditions, with a reducing system comprised of: metallic lithium and liquid ammonia in an inert organic solvent therefor at a temperature in the range of about -45° to -78°C for a sufficient time to stereoselectively produce the 7-beta compound V:

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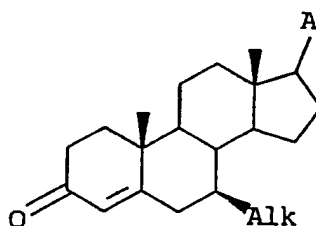


V;

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b) contacting compound V with a double bond isomerization agent in an inert organic solvent therefor, at a temperature of 40 to 65°C, under conditions in which the radical A is inert, for a sufficient time to form the isomerized compound VI.

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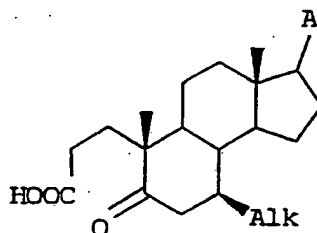
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VI;

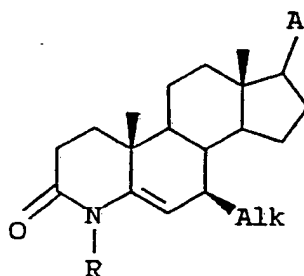
(c) contacting compound VI with an oxidizing agent in an inert solvent therefor, at a temperature in the range of 23 to 80°C, under conditions in which radical A is inert, for a sufficient time to form the seco acid VII:

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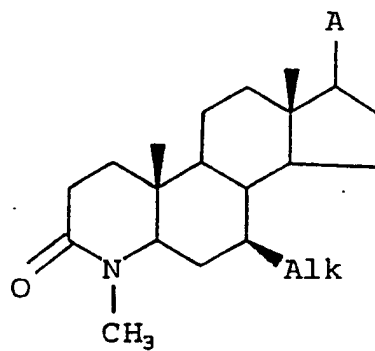
VII;

(d) contacting the seco acid compound VII with an amine of the formula: $R-NH_2$, wherein R is H, C_1-C_4 alkyl, benzyl or allyl, at a temperature of from 100 to 200°C in an inert solvent therefor, under conditions in which A is inert, to form the 4-aza-steroid VIII:

VIII;

(e) contacting VIII with a platinum catalyst in an inert organic solvent, at room temperature, under conditions where A is inert, for a sufficient time to form the 7-Alk 4-aza steroid VII:

- 45 -

VII.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04443

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 215/00

US CL :546/77

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/284; 546/77

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, B, 0,289,327 (HOLT et al.) 02 November 1988. See page 26	1-9
X Y	Jour. Med. Chem., Vol. 29, 1986 RASSMUSON, et al. "AZASTEROIDS: Structure Activity Relationships for Inhibition of 5 α Reductase and of Androgen Binding" pages 2298-2315. See page 2305 Scheme XIII, page 2308, col. 1, second full paragraph.	3-5 1-9
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☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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